



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,581	12/03/2003	Anthony D. Keefe	23239-544 (ARC-44)	3229
30623 7590 06/04/2010 MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C ONE FINANCIAL CENTER BOSTON, MA 02111				
EXAMINER				
STAPLES, MARK				
ART UNIT		PAPER NUMBER		
1637				
MAIL DATE		DELIVERY MODE		
06/04/2010		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/729,581

**Applicant(s)**

KEEFE ET AL.

**Examiner**

MARK STAPLES

**Art Unit**

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02/25/2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 101, 102, 182, 189, 190 and 195-210 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 101, 102, 182, 189, 190 and 195-210 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 01/14/2010
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. Applicant's amendment of claims 1, 101, 102, and 182; the submission of new claims 197-210; and the cancellation of claims 5-12, 14-17, 19, 20, 77-79, 81-85, 88, 90-94, 103-110, 112-114, 116-120, 122-127, 130-137, 139-148, 150-159, 161-174, 176-181, and 183-188 in the paper filed on 02/25/2010 are acknowledged.

Claims 1, 101, 102, 182, 189, 190, and 195-210 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**Rejections that are Withdrawn**

***Specification***

2. The objection to the disclosure is withdrawn, as Applicant has amended the disclosure to correct "Y639F" to "Y693F".

***Claim Rejections Withdrawn - 35 USC § 112 First Paragraph***

3. The rejection of claims 6, 7, 104, and 105 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in reciting "Y639F" is withdrawn. Applicant has amended the pending claims to recite claimed inventions of "Y693F" in Y639F/H784A double mutant T7 RNA polymerase for which there is written support.

4. The rejection of claims 1, 5, 9-12, 14-17, 19-20, 77-79, 81-85, 88, 90-94, 101-103, 108-110, 112-114, 116-120, 122-127, 130-137, 139-148, 150-156, 159, 159, 161-174, 176-190, 195 and 196 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. Applicant has amended the pending claims to recite claimed inventions of Y639F/H784A double mutant T7 RNA polymerase for which there is written support.

***Claim Rejections Withdrawn - 35 USC § 103(a)***

5. The rejection of claims 1, 5-7, 9-12, 14-16, 19-20, 77-79, 81-85, 88, 90-94, 101-105, 107-109, 112-114, 116-120, 122-127, 133-136, 139-147, 150-155, 158, 161-173, and 176-190 under 35 U.S.C. 103(a) as being unpatentable over by Pieken et al. (U.S. Patent 5,660,985 previously cited), Briebe et al. (Biochemistry (2000) 39:919-923 previously cited), Sousa et al (U.S. Patent 6,107,037 previously cited), Bishop et al. (1971, previously cited), and Chow et al. (1971) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment. The new claim amendments narrow the scope of the claimed invention by reciting only the specie which is the double mutant Y639/H784A mutant T7 RNA polymerase and not the formerly recited and broad genus of different modified RNA polymerases. Thus the applicability of the cited prior art is changed by the new and narrower claim amendments, especially in regard to the teachings of Bishop et al. concerning the genus use of both manganese and magnesium ions with different polymerases, but which teaching of Bishop et al. is no longer as strongly linked

to the new, sole, and narrowly claimed specie. Thus the narrowing in scope of the claimed invention to only one mutant polymerase and deletions of linked limitations through amendment required further consideration and a new search, resulting in new rejections, necessitated by amendment.

It is noted that Applicant is correct that the reference of Cook et al. (United States Patent 5,914,39 issued 1999) was incorrectly listed in the former rejection and is not listed above.

6. The rejection of claims 17, 110, 130-132, 137, 148, 159, and 174 under 35 U.S.C. 103(a) as being unpatentable over Pieken et al. (U.S. Patent 5,660,985), Briebe et al. (2000), Sousa et al (U.S. Patent 6,107,037), Bishop et al. (1971), and Chow et al. (1971) in view of Milligan et al. (Methods Enzymol. (1989) previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

7. The rejection of claims 8, 106, 157, 195, and 196 under 35 U.S.C. 103(a) as being unpatentable over Pieken et al. (U.S. Patent 5,660,985), Briebe et al. (2000), Sousa et al (U.S. Patent 6,107,037), Bishop et al. (1971), and Chow et al. (1971) as applied to claims 5, 103, and 134 above and in further view of Padilla et al. (2002 published December 15, 2002) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

**New Rejections Necessitated by Amendment**

**New Claim Rejections - 35 USC § 103**

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 101, 102, 182, 189, 190, and 195-210 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Pieken et al. (U.S. Patent 5,660,985 previously cited), Briebe et al. (Biochemistry (2000) 39:919-923 previously cited), Sousa et al (U.S. Patent 6,107,037 previously cited), Bishop et al. (1971, previously cited), Tabor et al. (1989), Tabor et al. (1995), Padilla et al. (2002 published December 15, 2002, previously cited), and Milligan et al. (Methods Enzymol. (1989) previously cited).

Pieken, Briebe, Sousa, Bishop, Tabor (1989), and Tabor (1995)

Pieken teaches methods of claims 1, 101, 102, 182, and 198 for identifying nucleic acid ligands that bind to a target molecule (see abstract) wherein the nucleic acid ligands comprise a 2'-OMe modified nucleotide (see claim 1 and claim 10, where 2' methoxy groups are expressly claimed),

(a) preparing a transcription mixture comprising a polymerase, modified dNTPs, wherein at least one NTP is 2' OMe NTP where N can be A, G, C, T or U (by teaching modified pyrimidine and purine bases can be 5-X and/or 2'-Y, here being 2'-Y only with Y being the methoxy group, see column 8 lines 38-63 and Figure 1), and specifically can be 2'-OMe guanosine (see the bottom left structure in Figure 1 and without the X substitution as provided for in column 1 line 25), magnesium and oligonucleotide transcription templates (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used and see claim 10, which requires the use of a 2' OMe NTP) including double-stranded DNA templates (see column 15 lines 55 and 56),

(b) preparing a candidate mixture of single-stranded nucleic acids by transcribing the one or more oligonucleotide transcription templates including double stranded templates (see Example 2) under conditions whereby the polymerase incorporates at least one of the one or more 2' O-methyl modified NTPs into nucleic acid molecules of said candidate mixture (see column 16, lines 13-35, where the T7 RNA polymerase is used to incorporate the NTPs and see claim 10, where the modified nucleotides are 2' O-methyl modified NTPs) wherein the stabilized single-stranded nucleic acids have a length in the range of 30-50 nucleotides by teaching a 2'-O-methyl stabilized

oligonucleotide of similar length to a 2'-amino oligonucleotide of 38 nucleotides (see Example 6),

(c) contacting the candidate mixture with said target molecule (see column 16, example 3, lines 13-35 and claim 1 ),

(d) partitioning the nucleic acids having an increased affinity to the target molecule relative to the candidate mixture from the remainder of the candidate mixture (see column 16, example 3, lines 13-35 and claim 1 ),

(e) amplifying the increased affinity stabilized nucleic acids which are oligonucleotides, in vitro, to yield a ligand enriched mixture of nucleic acids, whereby nucleic acid ligands of the target molecule are identified (see column 16, example 3, lines 13-35 and claim 1, and see column 20 lines 14-17 for the stabilized oligonucleotide).

Further regarding claims 1, 101, 102, and 182, Pieken teaches the use of 2' OH-guanosine which is a substituted guanosine (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used).

Regarding claims 1, 101, 102, and 182, Pieken does not specifically teach the use of modified polymerase and does not teach the use of Y639F or H784A T7 RNA polymerase. Pieken does not specifically teach the use of manganese and does not specifically teach the single stranded nucleic acids. Pieken does not specifically teach the double mutant Y639F/H784A T7 RNA polymerase.

Regarding claims 189 and 190, Pieken teaches repeating the claim steps (see claim 1).



Regarding claims 197, 199, and 200, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

Regarding claims 205 and 206, Pieken teaches the use of PEG (see column 15, line 49).

Regarding claim 207, Pieken teaches a variety of ratios and mixtures of modified to unmodified nucleotides (see column 13, lines 5-7).

Regarding claim 208, Pieken teaches the transcription mixture can further comprise spermidine (see Example 2).

Regarding claims 1, 101, 102, and 182, Brieba teaches that T7 polymerase mutants at position 784 preferentially utilize 2'-OH groups (see abstract) and position 639 mutants rapidly incorporate 2' modified nucleotides (see page 920). Brieba teaches transcribing oligonucleotides by teaching oligonucleotide transcript elongation (see Table 2). Brieba does not specifically teach the use of manganese and does not specifically teach the single stranded nucleic acids in the range of 30-50 nucleotides with incorporated 2'-O-methylribonucleotides. Brieba does not specifically teach the double mutant Y639F/H784A T7 RNA polymerase.

Regarding claims 1, 101, 102, and 182, Sousa also teaches the use of manganese and magnesium (see column 15, lines 44-48) but does not specifically teach the combination of manganese and magnesium ions. Sousa does not specifically teach the single stranded nucleic acids in the range of 30-50 nucleotides with

incorporated 2'-O-methylribonucleotides. Sousa does not teach away the combination of manganese and magnesium. Additionally, in light of the teachings of Bishop et al., Tabor (1989) and Tabor (1995), below, one of ordinary skill in the art would have been motivated to combine manganese and magnesium as this combination is superior to either manganese or magnesium alone. Sousa does not specifically teach the Y639F/H784A T7 RNA polymerase double mutant T7 RNA polymerase.

Regarding claim 210, Sousa teaches: "Preferably, the reactions also contain inorganic pyrophosphatase, which is known to increase the yields in *in vitro* transcription reactions" (see column 12 lines 41-43).

Regarding claims 1, 101, 102, 182, claims 201-203 each in part to  $Mg^{++}$  and  $Mg^{++}$ , and claim 209, Bishop et al. generally teach the use of combined manganese and magnesium for optimum performance of RNA polymerases in transcription by teaching: "The optimal conditions for assaying influenza (WSN) virion [ribonucleic acid] polymerase have been determined. The enzyme is maximally active . . . in reactions containing . . . 1 to 2 mM  $MnCl_2$ , . . . 8 to 10 mM  $MgCl_2$ , and the four ribonucleoside triphosphates at levels above certain delineated threshold values" (entire article, especially the first two sentences under the Discussion section on p. 69 and Figures 2 and 3) and by teaching *in vitro* synthesis/transcription with RNA polymerase (see Title, Abstract, and first sentence on p. 66). Furthermore, Bishop et al. teach concentration ratios of magnesium ions to manganese ions of 4 to 10 ( $8 \text{ mM } MgCl_2 / 2 \text{ mM } MnCl_2 = 4$  and  $10 \text{ mM } MgCl_2 / 1 \text{ mM } MnCl_2 = 10$ ) which overlaps the claimed concentration ratios

of magnesium ions to manganese ions of about 3 to 5. Bishop does not specifically teach the single stranded nucleic acids in the range of 30-50 nucleotides with incorporated 2'-O-methylribonucleotides. Bishop teaches virion polymerases and WSN virion polymerase with the combination of manganese and magnesium and teaches how to go about optimizing this and other polymerase conditions including incorporation of triphosphate nucleotides for maximal synthesis. Thus it would have been obvious to one of ordinary skill in the art to use the optimization approach of Bishop for other polymerases, especially for WSN virion RNA polymerases and RNA polymerase as given by Tabor (1989) and Tabor (1995) below. Bishop does not specifically teach the double mutant Y639F/H784A T7 RNA polymerase.

Regarding claims 1, 101, 102, 182, 201-203, and 209, Tabor (1989) teaches T7 DNA polymerase with a concentration of magnesium ions between 3 and 5 times greater than the concentration of manganese ions and reduces the discrimination against other analogs with modifications in the furanose moiety, the base, and the phosphate linkage including 2' OH NTPs (see 1<sup>st</sup> full sentence in the 2<sup>nd</sup> column on p. 4078) by teaching whereeach NTP, 2'-modified NTP, or 2'-OH modified NTP is present at a concentration of about 0.5 mM to 2.0 mM, the concentration of magnesium is about 5.0 mM to 9.6 mM and the concentration of manganese ions is about 1.5 mM to 2.9 mM and where the magnesium and manganese are incorporated together (Table 1 where Mn is present at 2 mM and Mg is present at 5 mM). Tabor (1989) does not specifically teach the double mutant Y639F/H784A T7 RNA polymerase.

Regarding claims 1, 101, 102, and 182, Tabor (1995) teaches a single hydroxyl group motif in T7 DNA polymerase is the molecular basis of its efficiency in discriminately enhancing incorporation of dideoxynucleotides which are modified nucleotides, while lowering the previously favored incorporation of deoxynucleotides which are unmodified nucleotides, and that the engineering of DNA polymerases by mutations results in this and other enhanced properties (see Abstract and see last paragraph on p. 6342 continued to p. 6343). Tabor (1995) relates these enhanced properties to RNA polymerases by teaching that: "Interestingly, this residue lies within a highly conserved motif shared by Pol II-type DNA polymerases and T7 RNA polymerase (2), suggesting that this motif plays a common role in forming the binding site for at least the ribose moiety" (see 4<sup>th</sup> sentence on p. 6343). Thus Tabor (1995) teaches T7 RNA and DNA polymerases have shared motifs and shared properties. Tabor (1995) in reference to Tabor (1989) also teaches: "The substitution of manganese for magnesium virtually completely eliminates discrimination by T7 DNA polymerase . . . ." (see 3<sup>rd</sup> sentence on the 3<sup>rd</sup> paragraph on p. 6343) and see reference no. 6). In summary Tabor (1995) teaches a tyrosine to phenylalanine mutation in T7 DNA polymerase which has less discrimination between different types of nucleotides with use of manganese by equalizing unmodified and modified nucleotide incorporation, teaches DNA T7 polymerase shares the tyrosine motif and properties with RNA T7 polymerase. Tabor (1995) at least suggests that a tyrosine to phenylalanine mutation in T7 RNA polymerase in the presence of manganese would give less discrimination between types of unmodified and modified nucleotides and further suggests, by referencing

Tabor (1989), a reduction in discrimination between the 2'-OH modified NTP's and unmodified NTP's in the presence of manganese.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T7 RNA polymerase mutants of Briebe in the methods of Pieken since Briebe notes that the polymerase with the double mutant is more likely to incorporate 2' O substituents (see abstract), and since Pieken would be motivated by this teaching to utilize the modified polymerase with superior properties for incorporation of the desired 2' modified nucleotides, including in the presence of both magnesium ions and manganese ions as taught by Bishop et al., Tabor (1989) and Tabor (1995) for incorporation of nucleotides.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the magnesium/manganese buffers of Sousa, Bishop et al., Tabor (1989) and Tabor (1995) in the methods of Pieken and Briebe. Sousa teaches regarding the use of manganese that "In Mn buffer both the w.t. enzyme and Y639F show a reduction in their sensitivity to substitution of dNTPs for rNTPs, consistent with an expectation of reduced substrate discrimination in Mn buffer (see column 22, lines 34-37)" and to use: "... inorganic pyrophosphatase ... to increase the yields in in vitro transcription reactions" (see column 12 lines 41-43). Bishop et al. teach the combined use of magnesium and manganese ions within the claimed ratio range to achieve optimum performance of *in vitro* transcription by RNA polymerases.

Tabor (1989) and Tabor (1995) teach that manganese reduces discrimination between modified and modified nucleotides in T7 polymerase, and at least suggest this also for the one claimed mutation of histidine to alanine in RNA T7 polymerase. Thus an ordinary practitioner would have been motivated to use manganese ions and magnesium ions in optimized concentrations for modified RNA polymerases in order to permit incorporation of the modified nucleotides expressly desired by Pieken and Briebe. And thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Padilla et al.

Bishop teaches that RNA polymerases can be optimized for a combination of manganese and magnesium ions.

Tabor (1989) and Tabor (1995) at least suggest histidine to alanine mutant T7 RNA polymerase and that this mutated T7 RNA polymerase in the presence of manganese reduces discrimination between unmodified and modified NTP's including 2' OH modified NTP's.

Pieken, Briebe, Sousa, Bishop, Tabor (1989) and Tabor (1995) do not specifically teach the double mutant Y639F/H784A T7 RNA polymerase.

Regarding claims 1, 101, 102, and 182, Padilla et al. specifically teach the Y639F/H784A T7 RNA polymerase double mutant T7 RNA polymerase for incorporating modified 2' NTP's including 2'-OMe NTPs into nucleic acids (entire article, especially p. 2

and Table 1) and thus generally but do not specifically teach 2'-OMe GTPs. Padilla et al. teach the double mutant is (1) tyrosine at position 639 mutated to phenylalanine and (2) histidine at position 784 to alanine (see 2<sup>nd</sup> paragraph on p. 1).

Regarding claims 195 and 196, Padilla et al. teach the double mutant Y639F/H784A T7 RNA polymerase for incorporating 2'-OMe NTPs and NTPs into nucleic acids (entire article, especially p. 2 and Table 1) and teach that this can be done without premature termination products and thus generally teach stabilized aptamers can be prepared with any percentage of 2'-OMe NTPs and NTPs including 80% of which are 2'OMe GTP and the remaining are 2'OH GTP; but do not specifically teach 2'OMe GTP and 2'OH GTP.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Pieken, Briebe, Sousa, Bishop, Tabor (1989) and Tabor (1995) do by using the double mutant Y639F/H784A T7 RNA polymerase for incorporating 2'-OMe NTPs into nucleic acids as suggested by Padilla et al. with a reasonable expectation of success. The motivation to do so is provided by Padilla et al. who teach the Y639F/H784A T7 RNA polymerase double mutant T7 RNA polymerase has: "... an enhanced ability to incorporate NMPs with bulky 2'-substituents into RNA. In reactions with 2'-OMe- or 2'-azido-modified NTPs yields of run-off transcripts, relative to reactions with the four canonical NTPs, are markedly increased with the double mutant and premature termination products are greatly reduced or eliminated" (see 1<sup>st</sup> sentence of the *Discussion* section on p. 3).

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Milligan et al.

Pieken, Briebe, Sousa, Bishop, Tabor (1989), Tabor (1995), and Padilla teach as noted above.

Pieken, Briebe, Sousa, Bishop, Tabor (1989), Tabor (1995), and Padilla do not specifically teach the use of GMP in T7 RNA polymerase reactions.

Regarding claim 204, Milligan teaches that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use GMP as taught by Milligan when performing the SELEX method of Pieken, Briebe, Sousa, Bishop, Tabor (1989), Tabor (1995), and Padilla using modified GTP such as 2'-O methyl GTP since Milligan states that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)." An ordinary practitioner would have been motivated to add GMP whenever low GTP amounts or modified GTP is being used in transcription reactions, in order to ensure the ability of the T7 RNA polymerase enzyme to prime the extension reaction.



**Conclusion**

11. No claim is free of the prior art.
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/  
Examiner, Art Unit 1637  
June 1, 2010